UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ASTELLAS INSTITUTE FOR REGENERATIVE MEDICINE, and STEM CELL & REGENERATIVE MEDICINE INTERNATIONAL, INC.,

Plaintiffs,

v.

IMSTEM BIOTECHNOLOGY, INC., XIAOFANG WANG, and REN-HE XU,

Defendants.

C.A. NO. 1:17-cv-12239-ADB

Leave to file granted on March 29, 2018

REPLY BRIEF IN SUPPORT OF PLAINTIFFS' MOTION TO DISMISS IMSTEM'S AND XIAOFANG WANG'S COUNTERCLAIMS

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TABLE OF ABBREVIATIONS

’321 patent	U.S. Patent No. 8,962,321 to Kimbrel, et al.
’551 patent	U.S. Patent No. 9,745,551 to Wang, et al.
’956 patent	U.S. Patent No. 8,961,956 to Kimbrel, et al.
Astellas	Astellas Institute for Regenerative Medicine
BM-MSC	Bone Marrow Mesenchymal Stem (or Stromal) Cell
Defendants	ImStem and Dr. Xiaofang Wang
EAE	Experimental Autoimmune Encephalomyelitis
ESC	Embryonic Stem Cell
HB-MSCs	Hemangioblast-derived Mesenchymal Stem (or Stromal) Cell
hESC	Human Embryonic Stem Cell
ImStem	ImStem Biotechnology, Inc.
MS	Multiple Sclerosis
MSC	Mesenchymal Stem (or Stromal) Cell
NOA	U.S. Appl. No. 13/905,526, Notice of Allowance (Dec. 17, 2014) (application issued as ’956 patent)
ImStem’s Opposition	Opposition to Plaintiffs’ Motion To Dismiss ImStem And Xiaofang Wang’s Counterclaims (D.I. 28)
Astellas	Astellas and SCRMI
Astellas’ Memorandum	Plaintiffs Astellas’ and SCRMI’s Memorandum In Support Of Their Motion To Dismiss Defendants ImStem’s and Xiaofang Wang’s Counterclaims (D.I. 22)
SCRMI	Stem Cell & Regenerative Medicine International, Inc.

I. INTRODUCTION

Defendants' ImStem and Xiaofang Wang (collectively "ImStem") Opposition confirms that Dr. Wang's only alleged contribution to the '956 patent was to suggest testing cells that ImStem concedes were invented by Drs. Kimbrel and Lanza, without any contribution from Dr. Wang, for a well-known property using a well-known method. Drs. Kimbrel's and Lanza's hemangioblast-derived mesenchymal stem cells ("HB-MSCs") and novel methods of making them are what distinguish the '956 patent from the prior art. Dr. Wang's alleged suggestion to test Drs. Kimbrel's and Lanza's novel cells in the well-known animal model of multiple sclerosis was routine experimentation within the grasp of any ordinarily skilled artisan.

ImStem does not dispute the key issues raised in Astellas and SCRMI's (collectively "Astellas") Memorandum: 1) that Drs. Kimbrel and Lanza developed the novel method for making HB-MSCs and sought out collaborators to test them for therapeutic utility; 2) that testing MSCs derived by different methods in the animal model of multiple sclerosis was well-known; and 3) that the only thing Dr. Wang allegedly contributed was to suggest that Astellas test the HB-MSCs made by their novel method in the same way MSCs made by different methods had been tested—namely using the known animal model for multiple sclerosis—and subsequently, to perform those tests. As explained in Astellas' Memorandum, taking these alleged facts as true for the purposes of this motion, there is no legal basis to find that Dr. Wang is a co-inventor on the '956 patent.

Instead of addressing the inventorship question directly, ImStem makes convoluted (and incorrect) arguments based on irrelevant or wrongly applied legal doctrines. First, ImStem points to an excerpt of the prosecution history of the '956 patent, taken out of context, to infer what the invention must be and argue that prosecution history estoppel (a doctrine concerning patent infringement, not inventorship) dictates the outcome. But the cited doctrine is irrelevant, and the

argument ignores that the examiner of the '956 patent expressly stated her views regarding what the invention is and why it was patentable in the notice allowing the patent to grant. (*See* D.I. 22 at 5 (quoting the Notice of Allowance).)

Second, ImStem reasons that either Dr. Wang is an inventor on certain claims of the '956 patent or those claims must be invalid for obviousness. But this is false, as the examiner explained, because the patent is limited to uses of the (independently patentable) HB-MSC's made by Astellas' novel methods—methods that were not known in the art, and which ImStem admits Dr. Wang did not invent.

Left with nothing else, ImStem argues that various factual disputes have to be resolved and that these disputes render Astellas' Motion premature. But this argument, too, fails because ImStem never explains how the factual disputes it identifies matter, given what is admitted or undisputed in the record.

II. ARGUMENT

1. ImStem Does Not Dispute the Key Issues Raised in Astellas' Memorandum

ImStem fails to dispute the key issues addressed in Astellas' Memorandum. ImStem admits that "Drs. Kimbrel and Lanza developed a new kind of MSC derived from hemangioblasts." (D.I. 28 at 2.) It concedes that "[P]laintiffs approached Dr. Wang (through a mutual contact, Dr. Shi-Jiang Lu) to *discuss testing the cells for MSC functionality*." (D.I. 28 at 2 (emphasis added).) And it nowhere disputes that MSCs were known to affect the immune system and had been tested as treatments for autoimmune disease, including multiple sclerosis. Indeed, the Background section of ImStem's own patent, which names Dr. Wang as an inventor, states:

> Importantly, MSCs have been found efficacious in the treatment of mice with experimental autoimmune encephalomyelitis (EAE), a well-recognized animal model of MS (Gordon et al., 2008a; Gordon et al. (2010); Morando et al. (2012); Peron et al. (2012); Zappia et al. (2005); Zhang et al. (2005)), as well as MS patients in

> clinical trials (Connick et al. (2012); Karussis et al. (2010); Mohyeddin Bonab et al. (2007); Yamout et al. (2010)).

('551 patent, 2:26-33 (D.I. 1-1 at 37); *see* D.I. 22, at 11-12 (quoting same).)

These factual allegations, accepted as true for the purpose of this motion, preclude ImStem from succeeding on its inventorship claim. They show that Dr. Wang's alleged "contribution" consists of, at best, explaining well-known concepts to the true inventors, Drs. Kimbrel and Lanza. (*See, e.g.*, D.I. 28 at 2, 6-7, 9-13, 16; *see also* D.I. 20, at Countercl. ¶¶ 2, 18, 33, 34, 40.) One cannot become a co-inventor by suggesting that a new type of piano be tested for the ability to play music or a new oven to bake a cake. The law has long recognized that contributing an idea that was well-known in the art is legally insufficient to support a claim of inventorship. (*See* D.I. 22 at 9-15 (citing cases).)

ImStem does not even try to distinguish most of the inventorship cases cited in Astellas' Memorandum. ImStem only attempts to distinguish one case, *Burroughs Wellcome Co. v. Barr Labs.*, 40 F.3d 1223 (Fed. Cir. 1994). (*Compare* D.I. 28 at 15-16 *with* D.I. 22.) *Burroughs Wellcome* confirms that inventors can rely on other scientists to test compounds for therapeutic potential as part of reducing an invention to practice without those other scientists qualifying as inventors. *Id.* at 1230. The non-inventor, collaborating scientists in *Burroughs Wellcome* "revealed for the first time that . . . [a compound] was exceptionally active against [a disease]." *Id.* That is precisely what Dr. Wang alleges he contributed to Astellas' invention: that he was the first to show that HB-MSCs had therapeutic potential in autoimmune disease. *Burroughs Wellcome* controls: under its holding, Dr. Wang is not an inventor on the '956 patent. While ImStem focuses on the existence of a draft patent application at the time the tests in *Burroughs Wellcome* were run, the Federal Circuit's larger focus was that the inventors had already conceived of what to test—what compounds to use and how to prepare them—giving them more than a

"general goal" of finding a method to treat AIDS. *Id.* Here, ImStem admits that Drs. Kimbrel and Lanza had already made and isolated HB-MSCs before and without any input from Dr. Wang. They already knew what to test: the novel HB-MSCs prepared by their inventive method. And Dr. Wang's own writings show that the "idea" of testing MSCs for treatment of autoimmune diseases, including multiple sclerosis, was already well-known in the field. [1]

2. ImStem's "Self-Defeating" Argument Misapprehends the Law and the '956 Patent

ImStem's argument that either Dr. Wang is an inventor or certain claims of the '956 patent he allegedly contributed to would have been obvious fails for the simple reason that it misunderstands and misapplies the law of obviousness.[2] ImStem's hyperbole about "self-defeating arguments" and "unwitting suicide" are unwarranted and irrelevant. ImStem argues that Astellas is "equating" prior art MSCs and those made by Astellas' methods. Not so. Astellas' position is not that HB-MSCs are identical to MSCs made by traditional methods. Instead, Astellas' argument is: once Drs. Kimbrel and Lanza had developed the new method for making HB-MSCs, it was standard practice to test those HB-MSCs to characterize how they were similar

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[1] ImStem cites *Falana v. Kent State University*, 669 F.3d 1349 (Fed. Cir. 2012) and *Vapor Point LLC v. Moorehead*, 832 F.3d 1343 (Fed. Cir. 2003) (per curiam), for the non-objectionable point that inventors need contribute to only a single claim in order to be named on a patent. (D.I. 28 at 8-9.) That is true as far as it goes, but it says nothing about the required substance of the contribution. As explained in Astellas' Memorandum, the contribution to a single claim must be significant in the context of the entire invention. (*See, e.g.,* D.I. 22 at 15-16.) Moreover, *Falana* illustrates a case in which the Federal Circuit found that a scientist who contributed to the method of *making* claimed chemical compounds was a co-inventor. 669 F.3d 1349, 1357-58. Here, ImStem admits that Dr. Wang did not contribute to the method of making HB-MSCs.

[2] This is not particularly surprising, as none of the three cases ImStem cites in its section on obviousness (Section C., D.I. 22 at 10-13) substantively address the law of obviousness. *Glaxo Wellcome, Inc. v. Impax Labs., Inc.,* 356 F.3d 1348, 1349 (Fed. Cir. 2004) (addressing infringement); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1310 (Fed. Cir. 2005) (addressing claim construction, infringement, and misappropriation of trade secrets); *Alpex Comput. Corp. v. Nintendo Co. Ltd.*, 102 F.3d 1214, 1223 (Fed. Cir. 1996) (addressing claim construction and infringement, and briefly discerning no error in a district court's determination on validity).

to or different from traditional MSCs.[3] And that routine characterization and testing was not inventive.

Moreover, while no one had previously tested HB-MSCs made by Astellas' method for efficacy against multiple sclerosis, the entire point of characterizing cells made by the new method was to determine the extent to which they were similar or different from MSCs made by existing methods. The "idea" of performing such an evaluation and its actual performance are not inventive contributions. (*See* D.I. 22 at 9-15.)

ImStem reaches into the realm of patent infringement case law, specifically the doctrine of prosecution history estoppel, in an attempt to mischaracterize the invention of the '956 patent. But prosecution history estoppel, which can apply where a patentee asserts infringement under the so-called "doctrine of equivalents," is irrelevant to inventorship, the only question before the Court. *See, e.g., Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki* Co., 535 U.S. 722, 734, 122 S. Ct. 1831, 1839, 152 L. Ed. 2d 944 (2002) ("Prosecution history estoppel ensures that the doctrine of equivalents remains tied to its underlying purpose.").

To make matters worse, ImStem's convoluted prosecution history estoppel argument relies on inferences about what the examiner thought was the invention of the '956 patent based on a "restriction requirement."[4] (*See* D.I. 28 at 6 ("[T]he PTO determined that the '526 application

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[3] Contrary to ImStem's arguments, method claims reciting treatment of a disease with a novel compound are not obvious just because a similar—even related—compound was known to treat the same disease. *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 860 (Fed. Cir. 2015) (method for treating an eye infection topically with a novel compound was not obvious when a related, similar compound was already being used to treat eye infections topically).

[4] ImStem's argument that electing to pursue claims related to manufacturing HB-MSCs in one patent (U.S. Patent No. 8,962,321) and claims directed to using those cells in a related patent (the '956 patent) demonstrate there must be two separate inventions fails. Having multiple patents with claims drawn to related inventions is not remarkable. *See, e.g.*, *Aventis Pharma Deutschland GmbH v. Cobalt Pharm., Inc.*, 355 F. Supp. 2d 586, 587-88 (D. Mass. 2005)

contained more than one invention and therefore issued a so-called 'restriction requirement'").) But the Court need not divine the examiner's thoughts—she explicitly stated what she considered to be the invention in her Notice of Allowance: Astellas' "hemangioblast-derived MSCs are found to be an allowable product" and therefore "the methods of use of said products are also deemed free of the art." (D.I. 22 at 5 (quoting Notice of Allowance).) It was the novelty and non-obviousness of the HB-MSCs that rendered these method of use claims patentable. The examiner then explicitly stated her reason for allowing the claims drawn to therapeutic uses of these cells: "Given the fact that the hemangioblast-derived MSCs have the same general properties as naturally occurring MSCs, it is reasonable to conclude that the hemangioblast-derived MSCs may be successfully used in all therapeutic application in which naturally occurring (i.e. bone marrow-derived MSCs) can be used." (D.I. 22 at 5 (quoting Notice of Allowance).)

The *core* of the invention, as evident from the examiner's reasons for allowance, is Astellas' novel HB-MSCs, made by their novel method. ImStem's argument that the novel HB-MSCs are irrelevant to the claims of the '956 patent—and that the patent is instead drawn to a use of those cells, (*see* D.I. 28 at 8)—is inconsistent not only with the Notice of Allowance, but also with the claim language itself. Claim 1 of the '956 patent includes the novel method of generating Astellas' HB-MSCs:

> 1. A method for treating a disease or disorder, comprising administering to a subject in need thereof an effective amount of mesenchymal stromal cells or a preparation of *mesenchymal stromal cells obtained by a method comprising culturing hemangioblasts under conditions that give rise to mesenchymal stromal cells*.

(considering whether compound and method-of-use patents owned by the same company were valid and infringed).

Dr. Wang did not suggest a new use for an existing compound. (*See* D.I. 28 at 6.) The HB-MSCs were not known—Drs. Kimbrel and Lanza invented them and the methods for creating them. It is the invention of this new cell type—not the idea of using them to treat a particular disease—at the core of the '956 patent.

3. All ImStem's "Disputed" Fact Questions Are Not Disputed or Not Relevant

Here, where ImStem pled that Dr. Wang made specific contributions to the topic of the '956 patent and those specific contributions were known in the prior art, it is appropriate to resolve the inventorship question on a Rule 12(b)(6) motion. (*See* D.I. 22 at 17-19 (citing cases).) ImStem does not dispute the key factual allegations here, *supra* part II.1. Instead, it attempts to distract the Court by reciting a laundry list of alleged factual disputes. None of ImStem's listed disputes are relevant to this motion:

- ImStem accuses Astellas of making a self-serving characterization of the prior art in the '956 patent's specification. (D.I. 28 at 14.) However, ImStem cannot credibly dispute that characterization of the prior art because Dr. Wang's own publications confirm it. (*Compare* D.I. 22 at 10-12 *with* D.I. 1-2 at 1 (citing, *e.g.*, Bai 2009, Gordon 2008, Zhang 2005, Karussis 2010, Mohyddin Bonab 2007, and Yamout 2010 to explain "[h]uman adult-tissue-derived MSCs have shown therapeutic utility in experimental autoimmune encephalitis (EAE) models of MS and in clinical trials for MS patients"); *see also* '551 patent at 2:11-57 (citing same articles as '956 patent).)

- ImStem mischaracterizes Astellas' argument to allege that there is a factual dispute regarding whether HB-MSCs are the same as MSCs. (D.I. 28 at 14.) But this allegation misses the point. The relevant question is whether testing to see similarities or differences between HB-MSCs and MSCs is inventive. It is not. (D.I. 22 at 9-15.)

- ImStem's assertion that Drs. Kimbrel and Lanza were "not familiar with MSC's anti-inflammatory abilities or their potential application in the area of autoimmune disease" is legally irrelevant. (D.I. 28 at 14, 16 (citing D.I. 20 at ¶¶ 18-20).)[5] Drs. Kimbrel and Lanza did not have to be familiar with, for example, MS or the

[5] ImStem admits that Drs. Kimbrel and Lanza approached Dr. Wang about testing their HB-MSCs for functionality. (D.I. 28 at 2.)

EAE model, and were allowed to rely on Dr. Wang's ordinary skill in the field to reduce their invention to practice without making him an inventor. (*See* D.I. 22 at 17.)

- ImStem disputes whether Dr. Kimbrel was a renowned authority on stem cells. (D.I. 28 at 15.) Whether she was a renowned authority is irrelevant to the question of whether Dr. Wang made a contribution to her invention.

- ImStem's assertion that "multiple sclerosis is the most important valuable clinical application" of the technology disclosed in the '956 patent is irrelevant. (D.I. 28 at 15.) It is facially apparent that multiple sclerosis is only one of many conditions mentioned in the patent. And commercial value is irrelevant to inventorship where the appropriate inquiry is whether the alleged contribution is "insignificant" in the context of the patent, (D.I. 22 at 7, 15-16); and contributing only what is well-known in the art is legally insufficient to meet this standard. (*See, e.g.*, D.I. 22 at 12 (citing *Caterpillar Inc. v. Sturman Indus., Inc.*, 387 F.3d 1358, 1378 (Fed. Cir. 2004); *Ruling Meng v. Ching-Wu Chu*, 643 F. App'x 990, 996; *Abbott Biotechnology Ltd. v. Centocor Ortho Biotech, Inc.*, 35 F. Supp. 3d 163, 171 (D. Mass. 2014); *Hess v. Advanced Cardiovascular Sys., Inc.*, 106 F.3d 976, 981 (Fed. Cir. 1997).)

The as-pled facts relevant to the inventorship question are undisputed.

III. CONCLUSION

For the foregoing reasons, Astellas requests that the Court dismiss ImStem's and Xiaofang Wang's Counterclaims.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on March 29, 2018, I caused a true copy of the foregoing document to be served upon all counsel of record via the Court's CM/ECF electronic filing system.

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